Rethinking psychosis

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I was glad to read Craddock and Owen's paper on the classification of the psychoses. There is much to admire

in their work: not only their genetics but their clinical methodology is "state of the art". In contrast to many earlier investigations, they recognise that, in nosological research, one must use course (longitudinal, "lifetime") data, not just episode symptomatology. They employ a detailed abstract of all clinical records, the best source for longitudinal psychopathology. They use multiple raters, not only for diagnoses, but also for symptoms and course: the raters review a typed narrative synopsis, there is regular training and review, and generating a consensus reduces error and enables reliability to be measured for actual ratings, not borrowed from those made long ago by co-trained experts. Their rating schedules cover many aspects of the natural history, as well as key symptoms. They use polydiagnosis for diagnostic categories with disputed definitions. The huge series needed for genetic studies makes more data available for nosological analysis than was available for earlier studies.

I am also in complete agreement about the need to rethink the classification of the psychoses, and jettison the Kraepelinian framework. In their work on schizoaffective psychosis, I was disappointed that acute polymorphic (cycloid) psychosis was not included in the polydiagnostic analysis, but I appreciate that this is just another taxon to be melted down. The strategy is no longer to search for genes matched with conventional categories. Rather the whole genome is to be related, by a giant canonical correlation, to all that can be identified and measured in psychopathology. The nosology of the psychoses qualifies for Sir Keith Peters' "area of medicine in which everything that is worth knowing has yet to be discovered". This generation of researchers will make these discoveries and bury the 19th century dogmas.

I need to take issue with the statement that "studies of symptom profiles …have failed to find a clear discontinuity between …the two categories". The source of this conclusion is a paper written by Kendell in 1987 (1). Four years later, we published an analysis of "lifetime" psychopathology (10 years, 3 episodes on average) in more than 300 patients. We condensed the psychopathology by maximum likelihood factor analysis, and searched for discontinuities by canonical variate analysis, deriving functions in one randomly selected half, and testing them in the other. We used a variety of criterion groups and found that the bipolar group was always distinct (2). Thus, it is not the "two entities principle" that needs revision. One entity (bipolar disorder) is a concept "worth knowing", and deserves an ICD and DSM rubric of its own. This would include mania and schizo-affective mania; cyclothymia and hyperthymia; hypomania provoked by electroconvulsive therapy and drugs; some catatonia; some recurrent familial endogenous depression; seasonal affective disorder; puerperal, menstrual, steroid and postoperative psychoses; perhaps cycloid psychosis, and the rare but quintessential 48-hour cyclers. Its boundaries need clearer definition, and no doubt genetics will identify a variety of antecedents, but bipolarity must be a final common path, based on a localised or biochemically specific brain phenomenon. It is the other category, "schizophrenia", that needs rethinking.

The discovery of genes that increase the risk of both "schizophrenia" and bipolar disorders is challenging. There is probably a mismatch between the number of genes involved, and the limited keyboard of psychopathology and temporal patterns. Symptoms can be condensed to delusions, auditory hallucinations, passivity experiences, depression, states of excitement (not all of which are "manic") and various forms of defect and social handicap; the temporal patterns are equally restricted. The number of genes has yet to be determined, but, if it is large, discords will inevitably be struck. But what does this predict for future genetic classifications? If there are no genes of major effect, but, instead, there are many which make a small contribution, it will not be possible to link a disease picture to a gene. What, then, will be the basis of the classification? Bipolarity, and perhaps delusional disorders, will survive, each with complex antecedents and with their biological basis clarified. But it is impossible to guess what kind and what level of brain dysfunction will define the chronic polymorphic psychoses. Will it be an anatomical dysfunction, or pathology at the micro-anatomical level – such as ideo-motor feedback loops (3) – or perhaps specific anomalies in the neurotransmitters themselves? Once the pathogenesis has been clarified, how will this be translated into clinical diagnosis and therapeutics? I look forward with fascination to the evolution of research and ideas in this area.

References

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3. Feinberg I, Guazzelli M. Schizophrenia – a disorder of the corollary discharge systems that integrate the motor system of thought with the sensory systems of consciousness. Br J Psychiatry 1999;174:196-204.